Appeal No. 2017-2508

United States Court of Appeals

for the

Federal Circuit

ATHENA DIAGNOSTICS, INC., OXFORD UNIVERSITY INNOVATION LTD., MAX-PLANCK-GESELLSCHAFT ZUR FORDERUNG DER WISSENSCHAFTEN E.V.,

Plaintiffs-Appellants,

– v. –

MAYO COLLABORATIVE SERVICES, LLC, dba Mayo Medical Laboratories, MAYO CLINIC,

Defendants-Appellees.

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF MASSACHUSETTS IN CASE NO. 1:15-CV-40075-IT INDIRA TALWANI, UNITED STATES DISTRICT JUDGE

REPLY BRIEF FOR PLAINTIFFS-APPELLANTS

DIMITRIOS T. DRIVAS
ADAM R. GAHTAN
ERIC M. MAJCHRZAK
VANESSA PARK-THOMPSON
WHITE & CASE LLP
1221 Avenue of the Americas
New York, New York 10020
(212) 819-8200

– and –

EMMETT J. MCMAHON
ANDREW J. KABAT
ROBINS KAPLAN LLP
800 LaSalle Avenue, Suite 2800
Minneapolis, Minnesota 55402
(612) 349-8500

Attorneys for Plaintiffs-Appellants

March 15, 2018

CERTIFICATE OF INTEREST

Pursuant to Federal Circuit Rule 47.4, Counsel for the Plaintiffs-Appellants certifies the following:

1. The full name of every party or amicus represented by me is:

   Athena Diagnostics, Inc., Oxford University Innovation Limited, and Max-Planck-Gesellschaft Zur Forderung der Wissenschaften e.V.

2. The name of the real party in interest represented by me is:

   Same as above.

3. All parent corporations and publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

Party	**Parent corporation and publicly held companies that own 10% or more of stock in a party**
Athena Diagnostics, Inc.	Quest Diagnostics, Incorporated
Oxford University Innovation Ltd.	The Chancellor, Masters, and Scholars of the University of Oxford
Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V.	N/A

4. The names of all law firms and partners or associates that appear for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

Emmett J. McMahon, Manleen K. Singh, Andrew J. Kabat, Lisa A. Furnald, Tara S.G. Sharp, ROBINS KAPLAN LLP,

Vicki G. Norton, DUANE MORRIS LLP,

Mathew B. McFarlane, LEICHTMAN LAW PLLC, and

Dimitrios T. Drivas, Adam R. Gahtan, Eric M. Majchrzak, Vanessa Park-Thompson, WHITE & CASE LLP.

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. *See* Fed. Cir. R. 47.4(a) and 47.5(b).

None.

Dated: March 15, 2018

/s/ Adam R. Gahtan
Adam R. Gahtan
Counsel for Plaintiffs-Appellants Athena Diagnostics, Inc., Oxford University Innovation Limited, and Max-Planck-Gesellschaft Zur Forderung der Wissenschaften e.V.

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

INTRODUCTION

Two precedential decisions issued after briefing in this appeal began reinforce critical legal and evidentiary standards that favor reversal of the district court's judgment of patent ineligibility. Those decisions direct that step two "innovative concept" determinations should be grounded in *facts* that relate to actual claim elements, alone or in combination, and that the party asserting ineligibility must prove those facts by clear and convincing evidence. They also confirm that this Court will reverse ineligibility holdings where a district court fails to create a satisfactory record, or ignores evidence that creates a dispute of fact as to whether claims reflect eligible innovations, further validating Athena's claim that the proceedings below were prejudicially inadequate. The district court deprived Athena of the procedural benefits due to the party opposing a motion to dismiss, and it failed to recognize or apply the evidentiary presumptions in favor of a patent's validity.

After repeatedly declaring its intention to convert Mayo's motion to dismiss into an inherently more fact-intensive motion for summary judgment, the district court unaccountably ignored evidence that showed at least a dispute of fact as to the nature – routine or not – of the asserted methods *as claimed*. This evidence included a detailed expert declaration, proffered in reliance on the court's intention to convert, that showed that the claimed methods were *not* routine or conventional.

The court ruled instead entirely on the basis of Athena's alleged "admissions" with respect to statements in the specification about background technology, which statements, moreover, the court explicitly considered only in isolation. The court described its own analysis as "very simplistic," and it expressed a desire to divest itself of jurisdiction as quickly as possible, suggesting that Athena would have "a lot more fun" in this Court. The consequences of the court's deficient procedure are evident in its deficient analysis. Mayo, which benefits from lack of an appropriate record, defends the court's approach.

With respect to step one, and contrary to Mayo's characterizations, the claims of U.S. Patent No. 7,267,820 (the "'820 patent") are not directed to the "correlation" between MuSK autoantibodies and MuSK-related diseases, or to the observation of that correlation. The claims recite concrete, physical steps in a laboratory method, traditionally eligible subject matter. That the method is useful in a diagnosis does not negate its eligibility. Nor is preemption of a natural law a "moot" consideration; it is, in fact, section 101's *sole* concern, and the asserted claims preempt neither the MG/MuSK autoantibody correlation nor even other methods of MG diagnosis that might rely on it. For this and the other reasons given in Athena's opening brief and below, those claims are patent eligible at step one, ending the analysis in Athena's favor.

For step two, Mayo relies on Athena's "admission" about immunoprecipitation and iodination. Those statements do not determine eligibility of the methods *as claimed*. Mayo's other attacks on the eligibility of claims 7-9 are obviousness arguments in support of which it has offered no evidence. Mayo also cannot explain away the district court's inappropriate substitution of the inventive concept analysis with a (faulty) written description analysis under Section 112(a). The asserted claims satisfy step two because they contain or represent inventive concepts: the use of a novel, synthetic molecule, the formation of a novel molecular complex, the first method of any kind for detecting anti-MuSK antibodies, and an innovative combination of steps.

ARGUMENT

I. THIS COURT SHOULD REVERSE BECAUSE THE DISTRICT COURT FAILED TO CONDUCT ADEQUATE FACT-FINDING

In its opening brief, Athena showed that it was reversible error for the district court to have ignored the extensive evidence that Athena proffered about the innovative nature of the asserted claims, and to rule based on isolated passages in the patent specification. (Opening Br. at 53-57) Mayo argues that the district court rightly ignored all other evidence, that the additional evidence was not properly before the court, and that it did not support Athena's position in any event. (Mayo Br. at 42-45) Since briefing began, this Court has issued two precedential decisions - *Berkheimer v. HP Inc.*, No. 2017-1437, 2018 U.S. App.

LEXIS 3040 (Fed. Cir. Feb. 8, 2018), and *Aatrix Software, Inc. v. Green Shades Software, Inc.*, No. 2017-1452, 2018 U.S. App. LEXIS 3463 (Fed. Cir. Feb. 14, 2018) – that confirm the necessity of reversal in light of the district court's look-away approach to fact-finding.

In *Berkheimer*, this Court reinforced the nature of and significant evidentiary burden associated with the eligibility inquiry:

> The question of whether a claim element or combination of elements is well-understood, routine and conventional to a skilled artisan in the relevant field is a question of fact. Any fact, such as this one, that is pertinent to the invalidity conclusion must be proven by clear and convincing evidence.

2018 U.S. App. LEXIS 3040, at *15 (citing *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 95 (2011)). The question also "goes beyond what was simply known in the prior art." *Id.* at *18. Thus, where the specification described "arguably unconventional inventive" computer-based archiving methods, and certain claims recited a "specific method" that possibly captured those concepts, there was necessarily a question of fact as to whether the method as claimed was "well-understood, routine, and conventional," notwithstanding what was known in the art about paper archiving. *Id.* at *19, 21-22. The district court should not have overlooked evidence – in that case, from the specification – that the *claimed* method was not routine. *Id*. at *19, 22-23.

Similarly, in *Aatrix*, this Court vacated the district court's Rule 12(b)(6) dismissal where *allegations* in the patentee's proposed amended complaint, and additional evidence (prior art, prosecution history), created a factual dispute as to "[w]hether the claim elements or the claimed combination are well understood, routine, conventional." 2018 U.S. App. LEXIS 3463, at *13. It was sufficient for vacating dismissal that that "[t]he 'data file' limitation *may* reflect . . . an improvement . . ." *Id*. at *17 (emphasis added). Mindful of the inferences and benefits due the party opposing a motion to dismiss, the Court concluded: "There are factual allegations in the second amended complaint, which when accepted as true, prevent dismissal pursuant to Rule 12(b)(6)." *Id*. at *18.

Here, despite having identified a dispute of fact in denying Mayo's initial motion (Appx285), and repeatedly declaring its intention to convert Mayo's renewed motion into one for summary judgment (Appx357-358; Appx361) – thereby inviting submissions such as the expert declaration from Dr. De Tomaso that Athena proffered – the district court not only failed to consider the available evidence, but seems actively to have avoided doing so.

Describing its own analysis as "very simplistic" (Appx308), the district court determined at argument that the specific anti-MuSK autoantibody detection assay *as claimed* was conventional and routine based on a background statement in the specification that iodination and immunoprecipitation, in general, were "standard

techniques in the art." (Appx318-319) The court confirmed that it was considering only those "isolated" statements, over Athena's objections that the issue was whether the assays *as claimed* were routine. (Appx319)

To show that the claimed assays were *not* routine, Athena provided the De Tomaso Declaration to accompany the renewed briefing. The district court ignored it. That was error, as this Court has just confirmed: dismissal is inappropriate where proffered evidence raises factual disputes as to "[w]hether the *claim* elements or the *claimed combination*" are routine. *See Aatrix*, 2018 U.S. App. LEXIS 3463, at *13 (emphasis added). The court's decision was especially unusual, and prejudicial, in light of its repeatedly stated intention to convert Mayo's renewed motion into one for summary judgment (Appx357-358; Appx361), a fact-dependent procedure.

It has long been clear, moreover, that a claim can be eligible even if all of its elements were known in the art. *See, e.g.*, *Diamond v. Diehr*, 450 U.S. 175, 188-89 (1981); *BASCOM Global Internet Servs., Inc. v. AT&T Mobility LLC*, 827 F.3d 1341, 1349-50 (Fed. Cir. 2016); *see also Exergen Corp. v. Kaz USA, Inc.*, No. 2016-2315/2341, 2018 U.S. App. LEXIS 6004, at *9, 11-15 (Fed. Cir. Mar. 8, 2018) (non-precedential decision affirming that combination of known claim elements was patent eligible inventive concept). Even if the court held the view that all elements in the asserted claims were known, therefore, the court was

required to determine, through fact-finding, whether the *combination* of those elements rendered the claim eligible. A finding that iodination and immunoprecipitation, in isolation, were known in the art, is hardly clear and convincing evidence that the *claimed* methods – the first of any kind for the detection of MuSK autoantibodies – were routine and conventional, particularly in light of the De Tomaso declaration. *See Berkheimer*, 2018 U.S. App. LEXIS 3040, at *15, 21-23. The claims do not cover immunoprecipitation or iodination *per se*. In fact, claim 6 does not involve either technique at all, and only claim 9 requires an iodinated molecule. (Appx48-49) Even without the declaration, giving Athena all inferences to which it is entitled, the court could not have resolved the factual dispute as to whether the assays *as claimed* were conventional or routine on a Rule 12(b)(6) motion. *See Aatrix*, 2018 U.S. App. LEXIS 3463, at *13, 17-18.

In addition to ignoring the declaration, the court abandoned its decision to convert Mayo's motion to one for summary judgment, another fact-aversive procedural move. The court also seemed eager to transfer jurisdiction to this Court, suggesting that Athena "may have a lot more fun with this in the [sic] front of the Federal Circuit than you are with me, but I am very simplistic here" (Appx308), and offering this Court's "fresh eyes" for a presumably more sophisticated analysis. (Appx315) The district court even suggested that Athena

should admit certain facts so that the court could rule against it and send the matter to the Federal Circuit:

> [I]f . . . you [Athena] would agree that iodination and immunoprecipitation are standard techniques in the art, but you think that's the wrong question, then maybe the most efficient way to do this would be for you to agree to that statement, I can enter judgment for the defendants based on that statement, and you can go up to the Federal Circuit and say, I'm completely wrong about the entire analysis, and not waste your clients' money on discovery.

(Appx306-307) The district court did indeed ask the wrong question, and it failed to develop the record on the right one.

Mayo endorses the district court's approach, and, indeed, argues that the court could have "invalidated" the asserted claims "based on those admissions [in the specification] without more," but, dramatically, credits the court for not doing so until Athena "conceded the truth of the patent's admissions on the record." (Mayo Br. at 43) Mayo makes the same mistake the district court made, but that the court would have avoided by considering the facts before it.

Mayo also argues that the district court acted within its discretion in disregarding Athena's expert declaration because it was not an "official public record, was not referred to in the complaint . . ., and is not a document central to Appellants' claim, that being the patent here." (Mayo Br. at 45) The First Circuit, whose procedural law governs, stresses the importance of a "practical, commonsense approach—one that does not elevate form over substance." *Beddall*

v. State St. Bank & Trust Co., 137 F.3d 12, 16–17 (1st Cir. 1998). In *Clorox*, for example, the First Circuit found it proper to review "advertising copy," submitted outside the bounds of the Lanham Act-based complaint, because it was "integral" to "assessing the sufficiency of the allegations in the complaint." *Clorox Co. v. Proctor & Gamble Commercial Co.*, 228 F.3d 24, 32 (1st Cir. 2000). The De Tomaso Declaration likewise directly addresses the patent-eligibility of claims 7-9, *i.e.*, the "sufficiency" of claims in Athena's complaint. At a minimum, the district court should have considered that declaration.

Mayo also wrongly suggests that, to be considered on a motion to dismiss, evidence outside the pleadings must be consistent with the underlying patent, comparing their own characterization of one aspect of Dr. De Tomaso's declaration to one item in the '820 patent specification. (Mayo Br. at 44-45) In fact, a court may consider evidence "consistent with the pleadings." *Comley v. Town of Rowley*, No. 17-cv-10038, 2017 U.S. Dist. LEXIS 179855, at *3 n.2 (D. Mass. Oct. 31, 2017) (considering Board minutes attached to plaintiff's opposition to a motion to dismiss) *(emphasis added*). Nothing about Dr. De Tomaso's opinion that the asserted claims reflect innovative concepts (e.g., Appx630-632) is inconsistent with Athena's allegations.

By disregarding the declaration, the district court failed to give Athena the benefit of all reasonable inferences to which it would otherwise be entitled at the motion to dismiss stage, and it committed reversible legal error.

II. STEP ONE: THE ASSERTED CLAIMS ARE NOT DIRECTED TO A NATURAL LAW

A. The asserted claims are not directed to a correlation between MuSK autoantibodies and MG, or to its "observation"

To practice the invention in claims 7-9, a person must physically *do* at least the following things: (1) "contact[] MuSK or an epitope or antigenic determinant thereof having a suitable label thereon, with said bodily fluid," (2) "immunoprecipitat[e] any antibody/MuSK complex or antibody/MuSK epitope or antigenic determinant complex from said bodily fluid," and (3) "monitor[] for said label on any of said antibody/MuSK complex or antibody/MuSK epitope or antigen determinant complex." (Appx48-49)

According to Mayo, however, the '820 patent claims "*plainly* are directed to *observing* the natural law the inventors allegedly discovered: the correlation between autoantibodies to MuSK and MuSK-related diseases." (Mayo Br. at 26 (emphases added); *see also*, *e.g.*, Mayo Br. at 20 ("claims cover methods for observing"); 22 ("claimed '820 invention involves 'seeing' . . . autoantibodies"); 23 n.3 ("claims are designed to observe or detect"); 24 ("claims are premised on observing")) As support, Mayo cites portions of the '820 patent's specification in

which the inventors (rightly) take credit for "uncover[ing] the correlation between anti-MuSK autoantibodies and certain neurotransmission disorders" and (rightly) describe MG diagnosis as a "particularly advantageous" "aspect" of the invention. (*Id.* at 21)

In fact, no form of "observe" or "see," or any like term, appears anywhere in the asserted claims. Mayo appears to rely on the preamble of independent claim 1, which Athena does not assert, but which identifies diagnosis as a goal of the method. (Mayo Br. at 20 ("each asserted claim depends from claim 1, which recites a method of diagnosis"); 21 ("diagnostic 'invention'"); 27 ("claimed methods are for diagnosing"); 28 ("claims are methods for diagnosis") Mayo also presumably relies on the "wherein" clause of the asserted claims, which describes the correlation. Preamble and wherein clauses are often non-limiting. *See Minton v. Nat'l Ass'n of Sec. Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed. Cir. 2003) ("A where[in] clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.") (citation omitted); *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1375 (Fed. Cir. 2001) (preamble phrase "for reducing hematologic toxicity" is non-limiting because it "merely express[ed] a purpose of reducing hematologic toxicity"). Regardless, methods of diagnosis are not *per se* ineligible, and, even construed as such, the asserted claims still require performance of concrete steps in the first-ever

laboratory technique for the detection of MuSK autoantibodies. Mayo wrongly dismisses those steps as irrelevant to the step one analysis, describing them, without discussion, as "known and standard detail" (Mayo Br. at 20), and "conventional techniques" (Mayo Br. at 28), that add nothing to the natural correlation. That is not so.

Discovery of the MuSK antibody/MG correlation put the inventors "in an excellent position to claim applications of that knowledge," *see Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048 (Fed. Cir. 2016) (quoting *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2120 (2013) (internal citation omitted)), which they did with their method for finding the relevant antibodies, in part through use of non-naturally-occurring radiolabeled MuSK. Even if the correlation between MuSK autoantibodies and MG relates ultimately to an MG diagnosis, the claims literally and unavoidably recite specific steps for *detecting antibodies*.

As this Court warned again one year ago,

> 'all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas.' We must therefore ensure at step one that we articulate what the claims are directed to with enough specificity to ensure the step one inquiry is meaningful.

Thales Visionix, Inc. v. United States, 850 F.3d 1343, 1347 (Fed. Cir. 2017) (citation omitted). Thus, in *Thales*, this Court reversed a holding of ineligibility

where the district court failed to distinguish between the natural law (known mathematical equations), and the invention as claimed, a "technique for measuring movement of an object on a moving platform," that relied on the law. *Id*. at 1348-49. The Court reiterated the lesson from *CellzDirect* that, "[a]t step one, 'it is not enough to merely identify a patent-ineligible concept underlying the claim; we must determine whether that patent-ineligible concept is what the claim is 'directed to.'" *Id.* at 1349 (quoting *CellzDirect*, 827 F.3d at 1050).

Here, Mayo improperly elides a natural phenomenon, the correlation between MuSK autoantibodies and MG, with the claimed invention, concrete steps in a method for detecting those autoantibodies. The asserted claims do not reduce to the correlation or its observation; in fact, the correlation plays no part in the detection steps. The claims do not become ineligible simply because there is a natural law related to its action or utility. *See Thales*, 850 F.3d at 1348-49.

Mayo also argues that the "level of direction (generic vs. specific) or type of step (concrete vs. mental) . . . is not the concern of *Alice* step one." (Mayo Br. at 23) Mayo is wrong, as explained in Athena's opening brief. (*See* Opening Br. at 34-38) If a claim is to a mental process, it is likely not patent-eligible at step one. *See Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1293 (2012) ("Phenomena of nature, though just discovered, *mental processes*, and abstract intellectual concepts are not patentable, as they are the basic tools of

scientific and technological work.") (emphasis added) (quoting *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972)). Claims that require concrete, physical steps – for example, laboratory steps – *are* patent eligible. *See CellzDirect*, 827 F.3d at 1047-48 ("new and useful laboratory technique" that required "an artisan to carry out a number of concrete steps"). Thus, in the cases Mayo relies on, the claims were ineligible where the method explicitly or in effect covered a purely mental step. *See Mayo*, 132 S. Ct. at 1297-98 (generically gathering data and then drawing inferences); *Cleveland Clinic Found. v. True Health Diagnostics LLC*, 859 F.3d 1352, 1356-57 (Fed. Cir. 2017) ("comparing" MPO levels); *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1376-77 (Fed. Cir. 2015) (because method "begins and ends with a natural phenomenon," it implicated only the mental processes of discovering the usefulness of detecting it).

Also contrary to Mayo's argument (Mayo Br. at 23), when a claim provides relatively greater "level of direction" for a method, it is more likely to be patent-eligible. In *McRO*, for example, the Court recognized the importance of examining whether claims "focus on a *specific means or method* that improves the relevant technology or are instead directed to a result or effect that itself is the abstract idea and merely invoke *generic processes*," *see McRO, Inc. v. Bandai Namco Games Am., Inc.*, 837 F.3d 1299, 1314 (Fed. Cir. 2016) (emphases added), and held the claims eligible at step one because they reflected a "specific implementation" and

were limited to a "specific process." *Id.* at 1316. Similarly, in *CellzDirect*, the Court emphasized that the claims-at-issue included a "number of concrete steps" in finding them patent-eligible. *See* 827 F.3d at 1047.

The cases from which Mayo argues that "concrete steps" do not favor eligibility are distinguishable. The claims in *Ariosa* required "manipulating blood samples; DNA amplification; detection with probe; nucleic acid analysis" (Mayo Br. at 28), but provided little to no guidance on *how* to perform each procedure. 788 F.3d at 1374. In *Cleveland Clinic*, the claims covered merely "comparing" MPO levels without any specific enumerated steps. 859 F.3d at 1356-57. In *Ambry*, the claims required only "hybridizing a BRCA1 gene probe" and "detecting the presence of a hybridization product," but provided no instruction for achieving those results and did not recite use of a *labeled* probe. *Univ. of Utah Research Found. v. Ambry Genetics Corp.*, 774 F.3d 755, 761 (Fed. Cir. 2014). In *Mayo*, the claims required "determining the level" of a certain chemical, but in no particular manner. *See* 132 S. Ct. at 1295. In *Genetic Technologies*, the claim required amplifying and analyzing steps that were "admittedly known." *Genetic Techs. Ltd. v. Merial LLC*, 818 F.3d 1369, 1377 (Fed. Cir. 2016).

Claims 7-9 are like the claims in *McRO* and *CellzDirect*, and unlike those in Mayo's cited cases, in that they require performance of *specific* steps in a *particular* laboratory method.

The appropriate guide for assessing eligibility of the asserted claims is *CellzDirect*. (*See* Opening Br. at 24-34) The inventors in *CellzDirect*, having "discovered that some fraction of hepatocytes are capable of surviving multiple freeze-thaw cycles," claimed "an improved process of preserving" them (in effect, a second freeze-thaw cycle). 827 F.3d at 1045. This Court held that invention patent-eligible at step one because it "require[d] an artisan to carry out a number of concrete steps," and because "the claims are simply not directed to the *ability* of hepatocytes to survive multiple freeze-thaw cycles." *Id.* at 1047-48 (emphasis added). As in *CellzDirect*, the '820 inventors discovered something important: autoantibodies to MuSK correlate to MG in patients that were un-diagnosable by tests for AChR antibodies. (Appx43, col. 1, ll. 54-61) Spurred by their discovery, the inventors developed and claimed the new methods recited in claims 7-9 of the '820 patent, for detecting MG antibodies. (Appx48-49) Those claims are no more to the *correlation* between MuSK autoantibodies and MG itself than the defined method in *CellzDirect* was to the "ability" of hepatocytes to survive refreezing. *See CellzDirect*, 827 F.3d at 1048.

Mayo argues that the claims in *CellzDirect* "*applied* the discovery of a natural property" (Mayo Br. at 26), whereas claims 7-9 recite the property itself, or the observation of it. (Appx48-49) No good faith reading of claims 7-9 supports that distinction. To practice the claimed invention, a person must physically

perform the specified method for detecting antibodies. That the antibodies "correlate with" certain diseases is a fact about the *antibodies*, not about the method for detecting them. Exactly as in *CellzDirect*, the discovery of a natural phenomenon prompted the inventors of the '820 patent to develop a novel and useful method, which they describe in the concrete steps of claims 7-9. Those claims are patent-eligible. *See CellzDirect*, 827 F.3d at 1047-50.

B. The asserted claims require the use of a novel, synthetic molecule and therefore cannot be "directed to" a law of nature

Claims 7-9 require the use of a synthetic molecule: labeled MuSK or labeled MuSK fragments. Mayo does not contest the novelty of those molecules, but argues that this Court "has repeatedly held that the mere use of a man-made material in a method claims [sic] will not save a claim under § 101." (Mayo Br. at 25) That is wrong.

In *Myriad*, the Supreme Court considered whether isolated DNA (which was physically identical to naturally-occurring DNA) and cDNA (also identical to naturally-occurring DNA except with non-coding portions removed) were patent-eligible. The Supreme Court held that isolated DNA was not patent-eligible, but that cDNA *was*, even though its sequence was dictated entirely by nature, because a "lab technician unquestionably creates something new when cDNA is made." *Myriad*, 133 S. Ct. at 2116-19.

Labeled MuSK is equivalent to cDNA for eligibility purposes.[1] It does not exist in nature, so that the '820 inventors "unquestionably create[d] something new," *see id.* at 2119, even if, as Mayo argues, certain specific labels are "conventional." (Mayo Br. at 25) A claim directed solely to labeled MuSK would therefore be patent-eligible. *See Myriad,* 133 S. Ct. at 2119. A claim to a method that includes that novel molecule is *also* patent-eligible. In *Ass'n for Molecular Pathology*, for example, this Court held a claim directed to "a method for screening potential cancer therapeutics" patent-eligible due to the "transformed, man-made nature of the underlying subject matter" in the claim. *See Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 689 F.3d 1303, 1335-36 (Fed. Cir. 2012), *rev'd in part on other grounds by,* 133 S. Ct. 2107 (2013). "The fact that the claim also include[d] the steps of determining the cells' growth rates and comparing growth rates [did] not change the fact that the claim [was] based on a man-made, non-naturally occurring transformed cell – patent-eligible subject matter." *Id.* at 1336.

Mayo's cases do not support their argument. The claim in *Ambry* was ineligible at step one because it was "directed to the . . . *abstract idea* of *comparing* BRCA sequences and determining the existence of alterations." *Ambry*, 774 F.3d at 763 (emphases added). The Court expressly declined to consider, in its step one

[1] This analysis applies to MuSK fragments or labeled-MuSK-fragments.

analysis, whether inclusion of a man-made probe rescued the claim from ineligibility: "We need not decide if *Mayo* is directly on point here because the method claims before us suffer from a separate infirmity: they recite abstract ideas." *See id.* at 762. In *Mayo*, likewise, the Supreme Court held the claims ineligible because they "simply tell doctors to gather data from which they may draw an inference in light of the correlations" – a purely mental step. *Mayo*, 132 S. Ct. at 1298. The decision did not turn on whether the inclusion of a non-natural element affected eligibility of a process.

Mayo quotes only a single sentence from *Genetic Technologies* (Mayo Br. 25), but omits this Court's actual reason for holding the claim ineligible: "While the man-made amplified non-coding DNA may have an 'altered methylation status,' its sequence *is identical* to that of *naturally occurring* DNA, unlike the cDNA held to be patent-eligible in *Myriad*." *Genetic Techs.*, 818 F.3d at 1377-78 n.3 (emphases added and internal citation omitted). *Genetic Technologies* does *not* stand for the proposition that man-made elements that *differ* from their natural-occurring analogues (as ^{125}I-MuSK differs from natural MuSK) are insufficient to render claims patent-eligible. In *Ariosa*, the claims were invalid because they "begin[ ] and end[ ] with a natural phenomenon." *Ariosa*, 788 F.3d at 1376. The method of claims 7-9, in contrast, begins with contacting a bodily fluid with *labeled* MuSK or a *labeled* MuSK epitope or antigenic determinant, requires

immunoprecipitating a complex of the *labeled* MuSK element, MuSK autoantibody, and secondary antibody, and ends with monitoring for the label on that complex. (Appx 48-49) Claims 7-9 thus neither begin nor end with a natural phenomenon.

C. The asserted claims of the '820 patent do not preempt a law of nature

Mayo argues that a preemption analysis is irrelevant, because, in Mayo's view, claims 7-9 are ineligible under the two-step *Mayo* test. (Mayo Br. at 40-41) In the alternative, Mayo argues that claims 7-9 "preempt diagnosis of MG through the detection of MuSK autoantibodies using 'standard' techniques 'known per se in the art.'" (*Id.* at 41) On both points, Mayo is mistaken.[2]

Preemption is *the* danger against which exceptions to patent eligibility guard: the "concern underlying the exceptions to § 101 is not tangibility, but preemption." *McRO*, 837 F.3d at 1315 (citing *Mayo*, 132 S. Ct. at 1301). As the Supreme Court puts it, "We have described the concern that drives this exclusionary principal as one of preemption." *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2354 (2014). Thus, although "the absence of complete preemption does not demonstrate patent eligibility," *Ariosa*, 788 F.3d at 1379, it is

[2] Although Mayo addresses preemption under step two of the analysis (Mayo Br. at 40-42), preemption is evidence of whether claims are directed to a natural law in the first place and properly considered at step one. *See McRO*, 837 F.3d at 1314-16.

evidence that challenged claims are *not* ineligible. *See, e.g.*, *Mayo*, 132 S. Ct. at 1294 (finding claims patent-ineligible because "upholding the patents would risk disproportionately tying up the use of the underlying natural laws, inhibiting their use in the making of further discoveries.").

Preemption is thus at the heart of ineligibility assessments. For example, although Mayo describes preemption as an afterthought in this court's *McRO* decision, it was in fact central: "[t]he narrower concern here is whether the claimed genus of rules preempts all techniques for automating 3-D animation that rely on rules." *McRO*, 837 F.3d at 1315-16 (claim *eligible* because it "does not preempt approaches that use rules of a different structure or different techniques"). Like the claims in *McRO*, claims 7-9 are limited to a "specific process," immunoprecipitation (claims 8 and 9 further limit the process to immunoprecipitation with a radioactive label and ^{125}I, respectively). By their terms, the claims do not "preempt approaches that use . . . different techniques." *Id*. at 1316. Dr. De Tomaso in fact suggested some alternatives. (Appx. 631-632, ¶¶ 110-111)

III. STEP TWO: INVENTIVE CONCEPTS IN THE ASSERTED CLAIMS RENDER THEM PATENT ELIGIBLE

A. The claims call for novel, non-natural molecules, which are innovative concepts that render the claims patent eligible

As discussed above (*supra*, Section I.B), claims 7-9 require the use of synthetic, novel chemical species and novel molecular complexes. These are inventive concepts sufficient to make the claims patent-eligible at step two. Mayo does not address this innovation directly, instead reiterating its incorrect step one argument that the inclusion of man-made elements can never be sufficient to render claims patent-eligible. (Mayo Br. at 38-40) That argument is no more availing in step two. (*See supra*, Section I.B)

Mayo also misreads *Myriad*. (Mayo Br. at 25-26) The Supreme Court held the cDNA claims eligible on grounds that the cDNA was merely "distinct" – not "markedly different" – from the naturally-occurring DNA. *Myriad*, 133 S. Ct. at 2119. The natural DNA in fact "dictated" the cDNA sequence, but, in making cDNA, the "lab technician unquestionably creates something new." *Id*. Mayo further errs in insinuating that the claims found invalid in *Ambry* and *Ariosa* recited the use of "labeled DNA." (Mayo Br. at 39) In neither case did the claims recite a labeled probe. Labeled MuSK, in contrast, like the cDNA in *Myriad*, is made by a lab technician and is "distinct" from natural MuSK.

B. The asserted claims describe a non-generic, non-conventional arrangement of steps and are therefore patent-eligible

Before the '820 patent, there was no method of any kind for detecting anti-MuSK autoantibodies, as Mayo does not dispute (*see, e.g.*, Mayo Br. at 19 (arguing that the novelty of Athena's claimed assay is irrelevant)), and the novel method entails more than the application of a routine, already-available method from the prior art. (Opening Br. at 41-44) The claimed method is therefore novel.

Mayo nonetheless argues that there are no innovations in claims 7-9, relying, as the district court did, on Athena's "admissions" below. (Mayo Br. at 29 (citing Appx44, col. 3, ll. 33-35, col. 3, l. 66 – col. 4, l. 12; Appx318-319)) In the '820 patent specification, Athena states that iodination and immunoprecipitation, in isolation, were "standard techniques in the art" and that certain immunological assay techniques were "known per se in the art." (Appx44, col. 3, l. 35; col. 4, ll. 10-11) Athena "admitted" at argument that iodination and precipitation *per se* were known, but, in the same breath, pointed out that the *claimed* inventions were *not* routine:

> [T]he application of that concept in this particular instance to the MuSK was different. . . . so - - and even that sentence right there again does not address the issue of routineness that is required by the Court.

(Appx319-320) Athena explained this distinction to the district court on numerous other occasions as well (*see, e.g.*, Appx319, Appx322-323; *see generally*

Appx581-633), and introduced evidence of the difference between known immunoprecipitation techniques and the asserted claims. (*See, e.g.*, Appx607, ¶ 57) Mayo produced nothing in opposition.

According to Mayo, the '820 patent describes "the previous use of each step" of the claim 7-9 method "only with a different ^{125}I-labeled antigen," it "explains that immunoprecipitation with radiolabeled AChR as the antigen had been used to diagnose MG in the majority of patients," and it cites "two decades-old scientific publications that describe previous use of radioimmunoassays to detect autoantibodies, again using radiolabeled AChR." (Mayo Br. at 30-31) Thus, Mayo argues, "anyone wishing to detect the presence of autoantibodies" could simply follow the teaching of those anti-AChR autoantibody methods. (*See* Mayo Br. at 31) This argument improperly invokes the law of obviousness as grounds for ineligibility, *see Mayo*, 132 S. Ct. at 1304 (courts may not "substitute §§ 102, 103, and 112 inquiries for the better established inquiry under § 101"), and Mayo offered no evidence whatsoever in support of its claim. In any event, as the '820 patent and Athena's expert make clear, the method in claims 7-9 is *not* a mere adaptation of the anti-AChR antibody detection technique. The anti-AChR method requires radiolabeling alpha-bungarotoxin toxin ("α-BuTx"), binding the α-BuTx to the antigen of interest (AChR), and only then performing immunoprecipitation steps. (Appx142; Appx149-150) There is no toxin whatsoever in the method of

claims 7-9, and, in fact, neither α-BuTx, nor any other known toxin, will bind MuSK. (Appx607, ¶ 57) The '820 inventors could not have followed the anti-AChR method described in the prior art on which Mayo relies. In their novel technique, among other differences, the label is affixed directly to the antigen.

"The inventive concept inquiry requires more than recognizing that each claim element, by itself, was known in the art. As is the case here, an inventive concept can be found in the non-conventional and non-generic arrangement of known, conventional pieces." *BASCOM Global*, 827 F.3d at 1350; *CellzDirect*, 827 F.3d at 1045, 1047-50 (noting that skilled artisans used the same freeze-thaw techniques in the prior art, for the same purpose, but holding eligible "an improved process of preserving hepatocytes" which differed only in that it recited a "second thaw"). That iodination and immunoprecipitation were known generally does not mean that a claim containing an immunoprecipitation step of an iodinated substrate is unpatentable. *Id.* Athena's "admission" does not address the particular immunoprecipitation technique claimed, even if the fundamentals were known generally, and iodination itself is not a required step of any the asserted claims (and only claim 9 requires an iodinated molecule).

Claims 7-9 are not, as Mayo argues, comparable to those held ineligible in *Cleveland Clinic*, *Ariosa*, and *Genetic Technologies*. (*See* Mayo Br. at 32-33) Mayo itself notes that in *Cleveland Clinic*, the court "pointed out that Cleveland

Clinic had not invented or claimed any new assay technique." (Mayo Br. at 32) Here, the inventors do claim a new assay – indeed, the first of any kind for MuSK autoantibodies – and define the steps with specificity. There was no suggestion in *Ariosa* and *Genetic Technologies* that the claims were to novel or non-generic methods.

C. The district court *did* improperly substitute a written description analysis for the appropriate step two test

Mayo argues that the district court's invocation of section 112(a) properly assessed whether Athena's "'complexity' argument" was consistent with "what the inventors taught in the specification and claimed" (Mayo Br. at 38), and that the court did not use it as a substitute for the step two analysis described in *Alice* and *Mayo*. (*Id.* at 37-38) The district court certainly did substitute one analysis for the other, for which the court's opinion is the best evidence. Directly addressing Athena's step-two argument that the claimed method was not routine, the court wrote:

> Plaintiffs' argument is unavailing. Patent applications are required to provide the precise description of the manner and process of making the invention. 35 U.S.C. § 112(a) ('The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connect, to make and use the same . . .')[.] None of the complexity to which Plaintiffs cite is described or claimed in the patent. While Plaintiffs argue that 'Production of 'MuSK or an epitope or antigenic determinant thereof having a suitable label thereon' required several steps that were neither well-known, not standard, nor conventional for MuSK,' this statement directly contradicts the language in the specification. In the specification, the inventors simply state that the 'suitable label' is ^{125}I or the like, and that iodination of the label is a standard technique. Furthermore, complexity alone does not make their method patentable.

(Appx11-12 (citations and alterations omitted))

It was reversible error for the court to evaluate eligibility according to a written description analysis. (Opening Br. at 47-51) In a written description analysis under § 112, moreover, a court analyzes whether "the specification shows that the stated inventor has in fact invented what is claimed, that he had possession of it." *AbbVie Deutschland GmbH v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1299 (Fed. Cir. 2014) (citation omitted). There is no requirement that a patent describe how difficult or complex the invention was to develop. In addition to doing the wrong analysis and then doing that analysis incorrectly, the court quoted and cited 35 U.S.C. § 112(a), which is an America Invents Act statute that does not apply to patents, like the '820 patent, that issued on applications filed prior to 2012. *See id.* at 1290 n.3.

IV. BECAUSE THE DISTRICT COURT FAILED TO ANALYZE CLAIM 6 – WHICH COVERS A DIFFERENT ASSAY FROM THAT RECITED IN CLAIMS 7-9 –ITS DECISION AS TO THAT CLAIM MUST BE REVERSED

Mayo argues that the district court's claim 6 "analysis" – which consists entirely of identifying claim 6 as "at issue" and reciting its elements – was sufficient because Athena consistently treated claims 6-9 "all together." (Mayo Br. at 46) According to Mayo, claims 7-9 were "representative" of claim 6. (*Id.* at 47) They were not. Mayo itself acknowledges that claim 6 recites an ELISA assay (*id.* at 8), while claims 7-9 are directed to immunoprecipitation (*Id.* at 30), and Mayo treated claims 6 and 7-9 separately in its motion to dismiss (*see* Appx381 (describing claims 7-9 as "radioimmunoassay claims") and Appx384 (describing claim 6 as the "ELISA claim" in a separate analysis)) Athena also never suggested or agreed that claims 7-9 were representative of claim 6. On these facts, the district court had no basis to treat claims 7-9 as representative of claim 6.

Perhaps more importantly, the district court's reason for invalidating claims 7-9 cannot possibly apply to claim 6. Iodination and immunoprecipitation simply do not play a role in the ELISA method that claim 6 recites. Nothing about Athena's "admission," which was the sole new development between the district court's denial of Mayo's initial motion and grant of its renewed motion, relates to claim 6.

Mayo also argues that Athena waived the right to contest the district court's decision regarding claim 6 because of its "failure before the district court to address Mayo's arguments as to claim 6." (Mayo Br. at 48) Mayo's motion to dismiss placed the patent-eligibility of claim 6 at issue. (*See* Mayo Br. at 46 (noting that Mayo's motion to dismiss "specifically addressed claim 6"); *see also* Appx384-385) The district court had an obligation to provide *some* analysis before finding it invalid. *See Plantronics, Inc. v. Aliph, Inc.*, 724 F.3d 1343, 1356-57 (Fed. Cir. 2013); *Osram Sylvania, Inc. v. Am. Induction Techs., Inc.*, 701 F.3d 698, 707 (Fed. Cir. 2012); *Nazomi Commc'ns, Inc. v. Arm Holdings, PLC*, 403 F.3d 1364, 1370-71 (Fed. Cir. 2005). None of the cases Mayo cites (Mayo Br. at 48), are analogous. In those cases, no party raised the waived issue until appeal. Here, the patent-eligibility of claim 6 has been at issue from the start. (*See* Mayo Br. at 46)

In addition, an "appellate court retains case-by-case discretion over whether to apply waiver." *Harris Corp. v. Ericsson Inc.*, 417 F.3d 1241, 1251 (Fed. Cir. 2005) (citing *Singleton v. Wulff*, 428 U.S. 106, 120 (1976)). Thus, even if there was a waiver (there was not), this Court may consider Athena's arguments. Here, claim 6 deserves separate, full, and fair consideration.

CONCLUSION

For the foregoing reasons, this Court should reverse or vacate the district court's decision granting Mayo's motion to dismiss and reinstate Athena's complaint. This Court should also find that claims 7, 8, and 9 of the '820 patent are directed to patent-eligible subject matter or, alternatively, remand the matter to the district court for further discovery concerning the technology underlying the '820 patent.

Dated: March 15, 2018

Respectfully submitted,

/s/ Adam R. Gahtan
Dimitrios T. Drivas
Adam R. Gahtan
Eric M. Majchrzak
Vanessa Park-Thompson
WHITE & CASE LLP
1221 Avenue of the Americas
New York, NY 10020
(212) 819-8200

Emmett J. McMahon
Andrew J. Kabat
ROBINS KAPLAN LLP
800 LaSalle Avenue
Suite 2800
Minneapolis, MN 55402
(612) 349-8500

Attorneys for the Plaintiffs-Appellants Athena Diagnostics, Inc., Oxford University Innovation Limited, and Max-Planck-Gesellschaft Zur

Forderung der Wissenschaften e.V.

United States Court of Appeals for the Federal Circuit

ATHENA DIAGNOSTICS, INC., et al. v. MAYO COLLABORATIVE SERVICES, LLC, et al., 2017-2508

CERTIFICATE OF SERVICE

I, Julian Hadiz, being duly sworn according to law and being over the age of 18, upon my oath depose and say that:

Counsel Press was retained by White & Case LLP, Attorneys for Appellant to print this document. I am an employee of Counsel Press.

On **March 15, 2018**, Counsel for Appellant has authorized me to electronically file the **Reply Brief for Plaintiffs-Appellants** with the Clerk of Court using the CM/ECF System, which will send notice of such filing to the following registered CM/ECF users:

Jonathan Elliot Singer
Fish & Richardson, PC
12390 El Amino Real
San Diego, Ca 92130
singer@f.com

John Cameron Adkisson
Elizabeth M. Flanagan
Phillip Goter
Deanna Jean Reichel
Fish & Richardson, PC
60 South Sixth Street, Suite 3200
3200 RBC Plaza
Minneapolis, MN 55402
adkisson@fr.com
EFlanagan@fr.com
goter@fr.com
reichel@fr.com

Counsel for Defendants-Appellees Mayo Collaborative Services, LLC (d/b/a/ Mayo Medical Laboratories) and Mayo Clinic

Upon acceptance by the Court of the e-filed document, six paper copies will filed with the Court, via Federal Express, within the time provided in the Court's rules.

March 15, 2018

/s/ Julian Hadiz
Counsel Press

CERTIFICATE OF COMPLIANCE WITH RULE 32

1. This brief complies with the type-volume limitation of Federal Circuit Rule 32(a) because:

   this brief contains 6,818 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(f) and Federal Circuit Rule 32(b), as determined by Microsoft Word.

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6) because:

   this brief has been prepared in a proportionally spaced typeface using Microsoft Office Word in 14 point Times New Roman font.

Dated: March 15, 2018

/s/ Adam R. Gahtan
Adam R. Gahtan
Counsel for Plaintiffs-Appellants Athena Diagnostics, Inc., Oxford University Innovation Limited, and Max-Planck-Gesellschaft Zur Forderung der Wissenschaften e.V.